A locus for isolated cataract on human Xp

P J Francis, V Berry, A J Hardcastle, E R Maher, A T Moore, S S Bhattacharya

Purpose: To genetically map the gene causing isolated X linked cataract in a large European pedigree.

Methods: Using the patient registers at Birmingham Women’s Hospital, UK, we identified and examined 23 members of a four generation family with nuclear cataract. Four of six affected males also had complex congenital heart disease. Pedigree data were collated and leucocyte DNA extracted from venous blood. Linkage analysis by PCR based microsatellite marker genotyping was used to identify the disease locus and mutations within candidate genes screened by direct sequencing.

Results: The disease locus was genetically refined to chromosome Xp22, within a 3 cM linkage interval flanked by markers DXS9902 and DXS999 (Zmax=3.64 at θ=0 for marker DXS8036).

Conclusions: This is the first report of a locus for isolated inherited cataract on the X chromosome. The disease interval lies within the Nance-Horan locus suggesting allelic heterogeneity. The apparent association with congenital cardiac anomalies suggests a possible new oculocardiac syndrome.

Conclusions: This is the first report of a locus for isolated inherited cataract on the X chromosome. The disease interval lies within the Nance-Horan locus suggesting allelic heterogeneity. The apparent association with congenital cardiac anomalies suggests a possible new oculocardiac syndrome.

Abbreviations: ADC, autosomal dominant cataract; NHS, Nance-Horan syndrome; VSD, ventriculoseptal defect

Figure 1 Chromosome Xp22 annotated with disease intervals coinciding with the Nance-Horan disease interval.
a large four generation family with isolated inherited congenital cataract. Members provided a full history and underwent a full clinical assessment by appropriate physicians.

Genotyping
Genomic DNA was extracted from EDTA sequestered blood samples taken with informed consent and local ethical approval using the Nucleon II DNA extraction kit (Scotlab Bioscience). PCR based microsatellite marker genotyping using the Genethon microsatellite markers at 5-10 cM intervals was performed as described previously.

Linkage analysis
Data were collated using the Cyrillic pedigree management software (version 2.1.3; Cherwell Scientific Publishing Ltd, The Magdalen Centre, Oxford Science Park, Oxford OX4 4GA). Two point lod scores were calculated using the MLINK programs. Although the disease appeared fully penetrant in heterozygous females, linkage analysis was modelled as an X linked recessive disorder with a gene frequency of 0.0001 assumed for the cataract locus.

RESULTS

The pedigree
Careful clinical examination showed that all affected males had required cataract extraction in the first few months of life with a uniformly poor outcome. This finding contrasted markedly with affected females who had very mild central nuclear opacities requiring no treatment until typically the sixth decade (table 1). Such observations raised the possibility that inheritance was X linked with full penetrance in heterozygotes. Unfortunately, none of the affected males had children and it was thus impossible to confirm the absence of male to male transmission. The complete pedigree is shown in fig 2.

The phenotype
In support of X linked inheritance, the appearance of the cataract was distinct from any ADC phenotype seen previously. The only phakic members of the family were female and, in each, cataracts were very slowly progressive, fan shaped, and nuclear in distribution (fig 3). There was no evidence of the features of NHS in any affected males or obligate carriers. Interestingly, however, four of the six affected males had a ventriculoseptal defect (VSD) and other cardiac developmental anomalies. No other family members gave a history of cardiac anomalies.

Linkage analysis
After excluding linkage to a number of markers on the X chromosome, we obtained significantly positive lod scores for marker DXS9902/GATA175D03. Indeed, only one recombinant (IV.1) is observed with this marker. Further linkage analysis provided strong evidence that the disease locus indeed lay centromeric to DXS9902, most likely residing between this

Table 1 Age and best corrected visual acuity for affected subjects in family 1

<table>
<thead>
<tr>
<th>Affected subject</th>
<th>Sex</th>
<th>Age in years</th>
<th>VA</th>
<th>Lens status</th>
<th>Age operated</th>
<th>VA</th>
<th>Lens status</th>
<th>Age operated</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.1 Female</td>
<td>72</td>
<td>6/6</td>
<td>Pseudophakic</td>
<td>68 years</td>
<td>6/6</td>
<td>Pseudophakic</td>
<td>68 years</td>
<td></td>
</tr>
<tr>
<td>III.3 Female</td>
<td>48</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.4 Female</td>
<td>46</td>
<td>6/9</td>
<td>NLO</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV.1 Male</td>
<td>23</td>
<td>NPL</td>
<td>Aphakic</td>
<td>3 months</td>
<td>CF</td>
<td>Aphakic</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>IV.2 Female</td>
<td>28</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V.1 Female</td>
<td>21</td>
<td>HM</td>
<td>Aphakic</td>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV.3 Male</td>
<td>17</td>
<td>CF</td>
<td>Aphakic</td>
<td>2 months</td>
<td>6/12</td>
<td>Aphakic</td>
<td>2 months</td>
<td></td>
</tr>
<tr>
<td>IV.5 Male</td>
<td>20</td>
<td>6/36</td>
<td>Pseudophakic</td>
<td>1 year</td>
<td>6/24</td>
<td>Pseudophakic</td>
<td>1 year</td>
<td></td>
</tr>
<tr>
<td>IV.6 Female</td>
<td>34</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td>NLO</td>
<td>6/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V.4 Male</td>
<td>8</td>
<td>6/12</td>
<td>Aphakic</td>
<td>At birth</td>
<td>6/60</td>
<td>At birth</td>
<td>At birth</td>
<td></td>
</tr>
</tbody>
</table>

NLO=nuclear lens opacities.

Table 2 Lod scores for linkage between the X linked cataract locus and polymorphic markers spanning the interval Xp22.32-21.13 ordered telomere to centromere. Lod scores are calculated modelling for X linked recessive transmission. Disease gene frequency 0.0001

<table>
<thead>
<tr>
<th>Marker</th>
<th>Lod score (Z) at recombination (θ) of</th>
<th>0</th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.2</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
<th>0.4</th>
<th>0.45</th>
<th>0.5</th>
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<tr>
<td>DXSGATA124B04</td>
<td>−∞</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXS1223</td>
<td>2.53</td>
<td>2.30</td>
<td>2.06</td>
<td>1.81</td>
<td>1.54</td>
<td>1.23</td>
<td>1.03</td>
<td>0.81</td>
<td>0.68</td>
<td>0.60</td>
<td>0.50</td>
<td></td>
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<tr>
<td>DXS7103</td>
<td>0.13</td>
<td>0.10</td>
<td>0.07</td>
<td>0.05</td>
<td>0.03</td>
<td>0.01</td>
<td>0.00</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−0.01</td>
<td></td>
</tr>
<tr>
<td>DXS1042</td>
<td>3.75</td>
<td>3.38</td>
<td>2.99</td>
<td>2.58</td>
<td>2.16</td>
<td>1.72</td>
<td>1.26</td>
<td>0.81</td>
<td>0.42</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−0.01</td>
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<tr>
<td>DXS1224</td>
<td>−∞</td>
<td>−∞</td>
<td>−0.54</td>
<td>−0.35</td>
<td>−0.30</td>
<td>−0.23</td>
<td>−0.17</td>
<td>−0.12</td>
<td>−0.08</td>
<td>−0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXS9902/DXSGATA175D03</td>
<td>−∞</td>
<td>−∞</td>
<td>3.04</td>
<td>2.78</td>
<td>2.45</td>
<td>2.08</td>
<td>1.67</td>
<td>1.22</td>
<td>0.77</td>
<td>0.35</td>
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<tr>
<td>DXS1195</td>
<td>0.49</td>
<td>0.43</td>
<td>0.36</td>
<td>0.30</td>
<td>0.25</td>
<td>0.20</td>
<td>0.15</td>
<td>0.11</td>
<td>0.07</td>
<td>0.03</td>
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<tr>
<td>DXS8036</td>
<td>3.64</td>
<td>3.29</td>
<td>2.93</td>
<td>2.54</td>
<td>2.15</td>
<td>1.73</td>
<td>1.30</td>
<td>0.87</td>
<td>0.47</td>
<td>0.17</td>
<td></td>
<td></td>
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<tr>
<td>DXS999</td>
<td>−∞</td>
<td>−∞</td>
<td>1.91</td>
<td>1.79</td>
<td>1.58</td>
<td>1.34</td>
<td>1.08</td>
<td>0.81</td>
<td>0.54</td>
<td>0.27</td>
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<tr>
<td>DXS7593</td>
<td>−∞</td>
<td>−∞</td>
<td>2.80</td>
<td>2.70</td>
<td>2.46</td>
<td>2.16</td>
<td>1.82</td>
<td>1.45</td>
<td>1.08</td>
<td>0.70</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

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For the abridged family for markers DXS7593, DXS999, DXS1223 and GATA124B04, no recombinants are observed at DXS7103 and DXS1224, though critically these markers are uninformative for IV.5, who is a recombinant with all adjacent microsatellites. As double recombination events are most unlikely over such small map distances, this subject is most probably a recombinant at DXS7103 and DXS1224 excluding linkage to this interval.

Haplotype analysis of the abridged family for markers within the Xp22 region is shown in fig 2 and lod scores in table 2.

**DISCUSSION**

This is the first description of a family with isolated, non-syndromic, X linked cataract. The existence of familial congenital cataract inherited in this way has been debated. The only possibly convincing X linked pedigree previously described is that by Krill et al. In this family, hemizygous males had sutured cataracts. The differential diagnosis of X linked cataract locus 107
linked cataract includes the syndromes of Nance-Horan, Lenz, and Lowe. It has been previously suggested that X linked isolated cataract may indeed be synonymous with Nance-Horan syndrome.6

In our family, X linked inheritance (with complete penetrance in heterozygous females) was suggested by affected subjects in successive generations, consistently severely affected males (requiring cataract surgery in the first few months of life), contrasting markedly with asymptomatic or mildly visually disabled carrier females. Unfortunately, there were no male offspring born to affected males. Further support was lent by the cataract phenotype that consisted of a sea fan of nuclear opacity in affected females and total opacity in hemizygous males, a combination of appearances not seen in autosomal dominant cataract.

Complex congenital cardiac anomalies were also noted in four of the six affected males and were not present in any unaffected subjects. The possibility that these abnormalities segregate with cataract formation in our family may prove instructive in identifying candidate genes. Several syndromes have been documented where congenital cataract and cardiac anomalies form a part. Arrhythmogenic right ventricular dysplasia associated with anterior polar cataract has been tentatively mapped to 14q22-23 and the association of cataract, microphthalmia, sepal heart defects, and deafness has been reported as a dominantly inherited syndrome.8,9 The oculo-facio-cardio-dental (OFCD) syndrome comprises cataract, microphthalmia, facial abnormalities, cardiac defect (atrial septal defect and VSD), and dental abnormalities.10,11 Interestingly, the condition appears to be X linked (lethal in hemizygous males), raising the possibility that a less deleterious mutation in the same gene might account for the spectrum of anomalies seen in our family.

To test the inheritance hypothesis, linkage analysis was performed across the X chromosome using the Genethon 5-10 cM microsatellite marker set. Linkage to markers at Xp22.2 was detected and the disease interval refined to lie between DXS9902 and DXS999 (Zmax=3.64 at θ=0 for marker DXS8036). The interval (CXN, congenital X linked nuclear cataract locus), which is less than 2.5 cM is encompassed by the Nance-Horan locus (DXS1053-DXS443).12,13 This most likely suggests that allelic heterogeneity within the same gene can result in either isolated cataract or cataract associated with other systemic anomalies and thus refines the disease locus. Alternatively, in accord with the Warburg hypothesis and with the recognition that a microdeletion of Xp22.3 results in ocular anomalies (microphthalmia, sclerocornea) and cardiac anomalies associated with linear skin defects,14 a lens gene and one or more other genes may reside within the disease interval.

Although the CXN locus is gene rich, there is no obvious cataract candidate gene. The retinoic acid induced -2 (RAI2) gene, previously considered a good candidate for Nance-Horan syndrome by Walpole et al.,15 lies outside the CXN disease interval.

This is the first report of a family with isolated cataract mapping to one of the sex chromosomes. Linkage to a refined region of the Nance-Horan locus in all likelihood reflects allelic heterogeneity and, given the possible segregation of cardiac anomalies with cataract in our family, it will be fascinating to explain the underlying genotype-phenotype correlation.

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X linked cataract locus


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